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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/975,139	10/10/2001	Volker Schellenberger	23623-7060	8883

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EXAMINER

DEJONG, ERIC S

ART UNIT PAPER NUMBER

1631

DATE MAILED: 10/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/975,139

Applicant(s)

SCHELLENBERGER ET AL.

Examiner

Eric S. DeJong

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 August 2005.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6, 11, 15-23, 25-29 and 31 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-6, 11, 15-23, 25-29 and 31 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

In future version of the claims, Applicants are notified that the claim identifier "(Canceled)" or "(Cancelled)" are sufficient to indicate the cancellation of a claim. As such future versions of claim 14, now canceled, should not recite "Please cancel claim 14" in the text of the claim.

Claims Rejections - 35 U.S.C. § 112 2nd Paragraph

The rejection of claims 11, 15-22, and 29 under 35 U.S.C. § 112, second paragraph as being indefinite is withdrawn in view of amendments made to the instant claims.

Claims Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 6, 11, 15-23, 25-27, and 31 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hatfield et al. (U.S. Patent Number 5,082,767). This rejection is maintained from the previous Office action and necessitated by amendment to the instant claims.

The instant claims are drawn to methods of creating a library of DNA sequences comprising providing a DNA sequence that encodes a protein of interest, a probability matrix for the protein, a constraint vector for the protein, applying the constraint vector to the probability matrix to produce a substitution scheme for at least two residues in the protein, and creating a library of at least 25 DNA sequences incorporating changes in the DNA sequence to produce the recommended substitutions.

Hatfield et al. discloses a method for determining the pattern of non-random codon pair usage of an organism (Abstract; and Figure 1). Nucleotide sequence data for an organism is obtained (instant claims 1 & 11 step a); Abstract). The number of codons represented in at least a portion of the sequence and the frequency of usage of at least some codons in the portion is determined (instant claims 1 & 11 step b) and claim 23 "probability matrix"; Abstract; Column 8, lines 16-18). The frequency of the expected number of occurrences of at least some codon pairs are determined (instant claims 1 & 11 step c) and claim 25 "constraint vector"; Column 2, lines 41-45; Column 8, lines 18-28). The expected number is then compared with the actual number of occurrences to determine relative codon pairing preferences (instant claim 1 step e), instant claim 11 step d), and instant claim 31 step a) "applying the "constraint vector" to the "probability matrix" to derive a recommended substitution scheme"; Column 8, lines 28-34). The authors indicate the application of the codon pair preferences (i.e. substitution scheme) in altering or constructing genes for the purpose of expression in other organism (i.e. *E.coli*) (instant claims 1, 11, and 31 "library is produced in a bacterial host"; Column 1, lines 14-19, 23-49, and 46-48). Hatfield et al. state the

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presence of a particular codon at one position has been shown to strongly influence the frequency of the occurrence of certain nucleotides in neighboring codons (instant claims 5 & 6 "structural characteristics" i.e. residue chemistry & proximity to the site of functionality; Column 2, lines 40-45). The disclosed method is a computer program (instant claims 26 and 27; Column 13, lines 7-15). Thus, Hatfield et al. anticipates the instantly claimed invention.

Hatfield et al. further set forth that the disclosed method "may alter codon pairs to change translation efficiency, a single codon may be altered, alternatively, two, three, four or even 20% or more codons pairs in the gene may be altered". See Hatfield et al., column 4, lines 45-49. In practicing the claimed invention, an expected frequency of each of the 3,721 (61^2) possible codon pairs may be utilized in generating a modified DNA sequence. Relying on a hypothetical nucleic acid sequence coding for a protein containing 150 codons, practicing the claimed on this hypothetical sequence allows for the generation of anywhere between 1 to $\sim 6.8 \times 10^9$ distinct modified sequences (20% of the 50 codon total yields 10 codon regions that may be altered, each altered codon position may further be modified to contain one of the 3,721 possible codon pairs). See Hatfield et al., column 8, lines 5-43. Therefore, the procedures set forth by Hatfield et al. anticipate the instantly claimed limitations of creating a library containing at least 25, 100, 250, 1000, 2500, and 10,000, DNA sequences or a library less than 10^9 , 10^6 , or 10^5 DNA sequences.

Claims Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 11, 15-28, and 31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hatfield et al. (U.S. Patent Number 5,082,767) in view of Blattner et al. (The Complete Genome Sequence of Escherichia coli K-12. Science. 05 September 1997, Volume 277, pages 1453-1462).

The instant claims are drawn to methods of creating a library of DNA sequences comprising providing a DNA sequence that encodes a protein of interest, a probability matrix for the protein, a constraint vector for the protein, applying the constraint vector to the probability matrix to produce a substitution scheme for at least two residues in the protein, and creating a library of at least 25 DNA sequences incorporating changes in

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the DNA sequence to produce the recommended substitutions. Further the instant claims recite the utilization of particular proteins of *E.coli* to be "esterase, dehydrogenase, and hydrolase" or "a protease, cellulose, lipase, hemicellulase, laccase, and amylase"

Hatfield et al. is herein applied from above (refer to 35 U.S.C. 102(b) Rejection). Hatfield specifically indicated the utilization of the *E.coli* genome in the disclosed invention (Column 16, lines 23-31), however, Hatfield et al. fails to specifically recite the utilization of particular proteins of *E.coli* to be "esterase, dehydrogenase, and hydrolase" or "a protease, cellulose, lipase, hemicellulase, laccase, and amylase".

Blattner et al. discloses the complete genome sequence of *E.coli* and indicates proteins of therein. For example, the authors indicate dehydrogenase (instant claims 2 & 3; page 1454, left column, line 57), hydrolase (instant claims 2 & 3; page 1457, right column, line 5), and receptor (instant claim 4; page 1459, right column, line 61) proteins.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to practice Hatfield et al. (U.S. Patent Number 5,082,767) in view of Blattner et al. to utilize the specific proteins (as indicated above) in the method of determining the pattern of non-random codon pair usage of an organism because Hatfield et al. indicates the utilization of the *E.coli* genome.

Response to Arguments

Applicant's arguments filed 05 August 2005 have been fully considered but they are not persuasive.

Applicants argue that amendments made to the instant claims, specifically the incorporation of the limitations from now canceled claim 14, that neither Hatfield et al. nor Blattner et al. anticipate or render obvious the instantly claimed invention. Applicants argument is not found persuasive for the reasons discussed above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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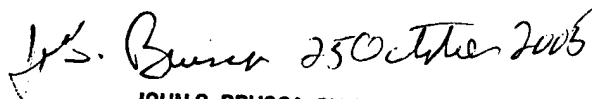
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Handwritten signature of John S. Brusca, dated 25 October 2005.

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER